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Modification of acetaminophen crystals. II. Influence of stirring rate during solution-phase growth on crystal properties in the presence and absence of *p*-acetoxyacetanilide

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Summary

Acetaminophen (P) crystals have been grown from pure aqueous solutions containing 0 and 500 mg · dm^{-3} *p*-acetoxyacetanilide (A) at various stirring speeds (200–400 rpm) and the physical properties examined. When A is omitted from the solutions, an increase of the stirring rate has no significant effects on the crystal habit (polyhedral prisms), but markedly raises the water content (by a factor of 10), lowers the enthalpy of fusion, ΔH^f, melting point, T_m, and entropy of fusion, ΔS^f, (by 8–18%, 0.6–1.65% and 7.4–16%, respectively) and decreases and then increases the intrinsic dissolution rate (*IDR*) of the P crystals. However, in the presence of A, the crystals assume an acicular morphology, independent of the agitation rate of the solutions. Whilst eliciting no further changes in the habit of these crystals, application of more vigorous stirring to the solutions leads to a moderate decrease in the uptake of A, a slight increase in water content, a slight decrease in the ΔH^f, T_m and ΔS^f as well as an initial reduction and a subsequent rise of *IDR*. Compared with the polyhedral prisms crystallized in the absence of A, these crystals invariably demonstrate a considerably higher *IDR*, consistent with their needle-like habit and much lower water content. These observations demonstrate the pharmaceutical significance of agitation during crystallization in modulating the physical properties and aqueous dissolution rate of the P crystals.

Introduction

Crystal habit (i.e. shape) and crystal imperfections (e.g. point defects and dislocations) arise during and/or after crystallization and could play commanding roles in the processability of pharmaceutical raw materials as well as the efficacy and performance of the final solid dosage forms (for review, see York, 1983).

Previous work in our laboratory has demonstrated that crystallization of acetaminophen, P, from aqueous solutions containing various concentrations of *p*-acetoxyacetanilide, A, both a proposed prodrug and synthetic impurity of P, systematically alters the habit and imperfections of the crystals, the latter being evidenced by changes in their water content, uptake of A, density, fusion energetics and intrinsic dissolution rate (Chow et al., 1985; Duncan-Hewitt and Grant, 1986). To

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further probe the mechanisms of the incorporation of the both A and water and their roles in regulating the crystal morphology and crystal defects of P, similar studies have since been extended to the crystallization variables, stirring rate and initial supersaturation of the solutions. The present paper examines the influence of stirring rate alone or with A on the crystal growth and various related physical properties of P. The rate of agitation during crystallization is expected to influence the kinetics of mass transfer of the major component, i.e., P, and the minor components, i.e. A, and water, to different extents (Mullin, 1972; Ny'vlt 1971, 1978) and hence to exert subtle differences on the physical properties of the crystals.

Materials and Methods

Reagents and materials

The sources and chemical purities of P, acetonitrile and methanol as well as the preparation procedure for A have been reported previously (Chow et al., 1985). Phenacetin (*p*-ethoxyacetanilide, m.p. 144–145 °C) was of purest reagent grade supplied by J.T. Baker and was used as received. Water was double-distilled in an all glass apparatus.

Batch crystallization from water

Essentially the same batch crystallization procedure detailed by Chow et al. (1985) was used with the following modifications. P (9 g) was crystallized from water (390 cm^3) containing 0 or 500 $mg \cdot dm^{-3}$ A at various stirring speeds (200–400 rpm).

Incorporation of additive into growing crystals

The uptake of A by P crystals was determined by high-performance liquid chromatography using an HPLC pump (Gilson model 302), a variable wavelength detector (Gilson, Holochrome), a 3×3 reversed-phase column (Perkin-Elmer, C_{18}, 33×4.6 mm). The mobile phase was composed of 18% methanol and 82% water, which was pumped at 2 $cm^3 \cdot min^{-1}$. The UV detector was set at $\lambda = 240$ nm. The doped crystals (ca. 50 mg) and phenacetin as the internal standard were dissolved in acetonitrile (5 cm^3) and 2 mm^3 samples were injected (0.02–0.12 μg A + 0.24 μg phenacetin). The retention times of P, A and phenacetin were 0.74, 3.6 and 7.5 min, respectively. Linearity of the detector response with the amount of A within the concentration range used was checked by calibration plots using different amounts of A and a fixed amount of phenacetin.

Differential scanning calorimetry

Measurement of the enthalpy of fusion, ΔH^f and melting point, T_m, by differential scanning calorimetry (DSC) and calculation of the entropy of fusion, ΔS^f, of the crystals were carried out as described by Chow et al. (1985) with the following slight modifications. Instead of cutting and weighing, integration of the peak areas in the thermograms was determined electronically. A microcomputer (Apple IIe) equipped with a data acquisition/control board (ADALAB, Interactive Microware, PA 16801) was interfaced with the Perkin Elmer DSC-2C calorimeter. Using Chromatochart software (Interactive Microware) the data obtained were processed. The precision of this procedure, as determined by 6 repeated measurements of the area of the melting endotherm of the indium standard, is 0.05–0.20%.

Microscopic techniques, X-ray powder diffraction, water determinations, surface area measurements and dissolution studies

Hot-stage microscopy (HSM), optical microscopy, scanning electron microscopy (SEM), X-ray powder diffraction, water content determinations, specific surface area measurements and dissolution studies of the crystals were performed as reported by Chow et al. (1985).

Results and Discussion

Uptake of additive and water

An increase in the rate of stirring of the defined crystallization solutions at 500 $mg \cdot dm^{-3}$ A diminishes the uptake of A by the growing crystals ($x_A = 0.0017$–0.0014; Fig. 1). This observation indicates that, although stirring enhances the mass transport of A to the surface of the crystals, it

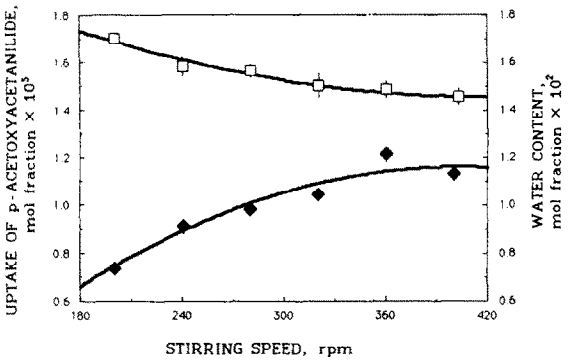

Fig. 1. Uptake of *p*-acetoxyacetanilide, A (□), and water (◆) by acetaminophen crystals grown in the presence of 500 mg·dm^{-3} A from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. The vertical bars represent the standard deviations of triplicate determinations. Each data point for the water content is the mean of duplicate measurements.

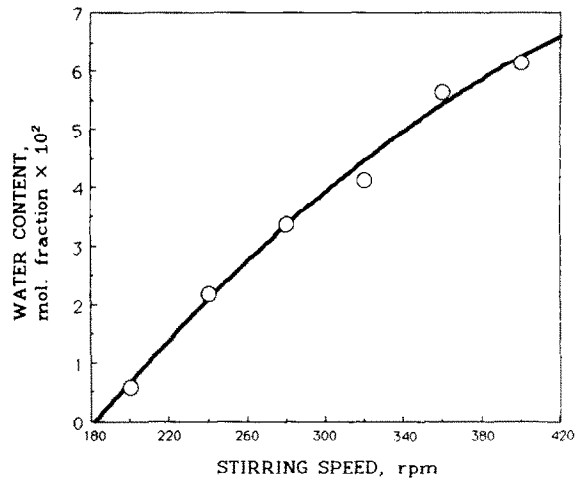

Fig. 2. Uptake of water by acetaminophen crystals grown from pure aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. Each data point is the mean of duplicate determinations. The variation between measurements is less than 6%.

opposes the incorporation of A into the crystal lattice of P. In explanation, the uptake process depends not only on the frequency of the A molecules arriving at the crystal surface, but also on their orientation with respect to the P molecules forming the lattice. In other words, a surface reaction-controlled mechanism becomes predominant at high stirring rates.

Associated with the reduced uptake of A are slight increases in the amount of water incorporated into the crystals of P ($x_w = 0.0074$–0.0113; Fig. 1), indicating increasing competition of water for the adsorption sites of A in the lattice. Increasing rate of stirring of the crystallization solutions in the absence of A causes the water content of the crystals to rise considerably (by a factor of 10; Fig. 2). The overall results suggest that the incorporation of water, though predominantly mass transport-determined, can be rate-limited by the essentially surface reaction-controlled uptake of A.

Crystal morphology and particle size

The stirring rate during crystallization in the presence of 500 mg · dm^{-3} of A has no significant effect on the length (326 ± 97 μm), width (30 ± 38 μm) and the acicular morphology of the crystals (Table 1), although Fig. 3 shows a slight trend in the ratio length/width. Crystals grown in the absence of A assume a polygonal prismatic habit whose dimensions also appear to be little affected by the stirring rate of the solutions (Table 1).

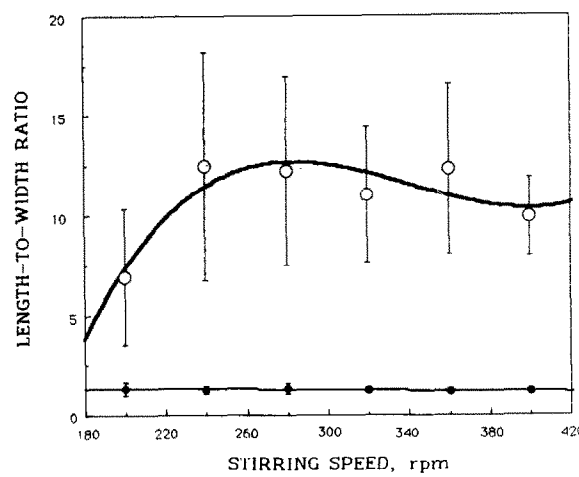

Fig. 3. Length-to-width ratios of acetaminophen crystals grown in the presence (○) and absence (●) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. The vertical bars represent the standard deviations of twenty measurements.

TABLE 1

Lengths and widths of acetaminophen crystals grown in the presence and absence of 500 mg · dm^{-3} p-acetoxyacetanilide, A, from aqueous solutions at initial supersaturation of 6.63 g · dm^{-3} and at various stirring speeds

Stirring speed (rpm)	In the presence of 500 mg · dm^{-3} A (μm ± S.D. *)		In the absence of A (μm ± S.D. *)	
	Length	Width	Length	Width
200	408.9 ± 254.2	85.8 ± 51.0	138.0 ± 67.5	114.7 ± 69.9
240	190.5 ± 114.8	16.8 ± 8.6	220.8 ± 70.5	185.3 ± 61.9
280	385.4 ± 217.3	42.0 ± 34.6	278.3 ± 120.2	220.4 ± 104.9
320	308.8 ± 96.3	29.9 ± 11.0	295.6 ± 126.0	246.8 ± 112.5
360	346.0 ± 180.5	29.7 ± 15.7	258.7 ± 119.1	230.3 ± 109.6
400	245.5 ± 110.9	24.9 ± 10.5	273.6 ± 119.8	244.2 ± 114.7

* Indicates standard deviation of twenty measurements.

In line with its inhibition of crystal growth reported previously (Chow et al., 1985), the presence of A in the solutions reduces the crystallization yield obtained at 2 h, which can, however, be raised by stirring the solutions more vigorously (Fig. 4). Under these circumstances, faster crystallization, as indicated by higher growth yield harvested at 2 h, is strongly associated with higher water content and lower uptake of A, further fortifying our previous inference that the mechanisms of the incorporation of both A and water are largely governed by the kinetics of crystal growth. However, this does not appear to be the case for the crystals grown in the absence of A at high stirring speeds, for which the water content of the crystals has increased considerably (Fig. 2), but the crystallization yields have dropped significantly (Fig. 4). This suggests that the incorporation of water into the crystals under these conditions may involve more specific and more complex mechanisms, which are not predictable or explicable by the differences in crystallization rate alone. These observations also indicate that the mechanisms of the crystal growth of P under the influence of high stirring rates can change from being surface reaction-controlled in the absence of A to being mass transport-determined in the presence of 500 mg · dm^{-3} A. In explanation, the inhibitory effects of A on the crystallization rate can be antagonized by an increase in the agitation rate during growth.

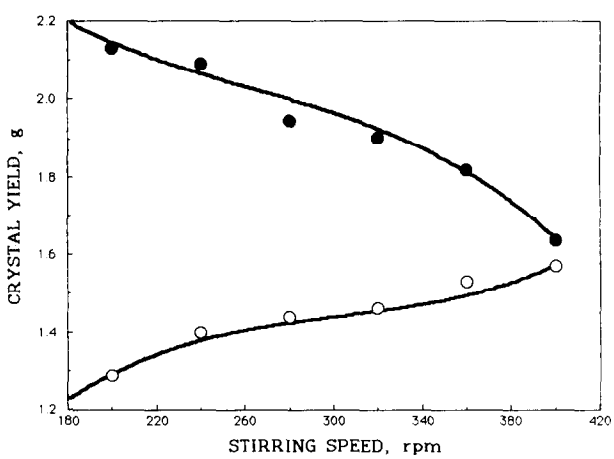

Fig. 4. Yields of acetaminophen crystallized in the presence (○) and absence (●) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. Each data point is the mean yield of 5 batches.

Fusion thermodynamic properties

Increasing the stirring rate during growth in the presence of 500 mg · dm^{-3} A slightly reduces ΔH^f (Fig. 5), and T_m and ΔS^f of the crystals (Table 2a), in parallel with slight increases in water content (Fig. 1). However, in the absence of A, ΔH^f (Fig. 5) and T_m and ΔS^f of the crystals (Table 2b) decreased considerably (by 8–18%, 0.6–1.65% and 7.4–16%, respectively) with increasing agitation of the solutions, consistent with large increases in water content (Fig. 2). The results reinforce our previous notion that a low mole fraction of A in the crystals, although creating little disruption by itself, is capable of modulating the incorporation

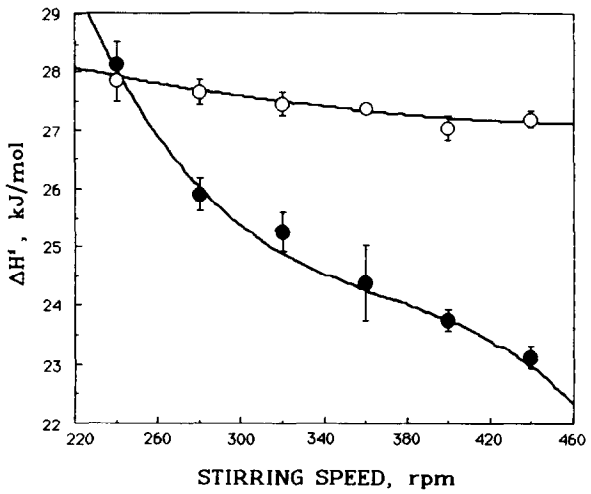

Fig. 5. Enthalpies of fusion, ΔH^f, of acetaminophen crystals grown in the presence (○) and absence (●) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. The vertical bars represent the standard deviations of quadruplicate determinations.

of the much larger amounts of the major disrupter, water, into the lattice, thereby controlling the energy and entropy of the crystals (Chow et al., 1985).

To quantify the extent of crystal lattice imperfections induced by A and/or water under either of the aforementioned crystallization conditions, the ideal molar entropy of mixing, ΔS^m_{ideal}, of the components (P, A and/or water) of the impure crystals (Eqn. 1) was calculated and used to determine the "disruption index" (*d.i*) which is defined as the negative slope derived from the linear regression of ΔS^f on ΔS^m_{ideal} (Eqn. 2; Chow et al., 1985; York and Grant, 1985). The parameters and statistics of the latter analysis are shown in Table 2, while the linear plots are shown in Figs. 6a and b.

The ideal molar entropy of mixing of the various components of the doped crystals is given by:

$$\Delta S^m_{ideal} = -R(x_P \ln x_P + x_A \ln x_A + x_w \ln x_w) \quad (1)$$

TABLE 2

Melting points, T_m, and molar entropies of fusion, $\Delta S^f = \Delta H^f / T_m$, of acetaminophen crystals, and calculated ideal partial molar entropies, $\bar{S}_j = -Rx_j \ln x_j$, ideal molar entropies of mixing, $\Delta S^m_{ideal} = \Sigma \bar{S}_j$, of the components in the crystals and the statistics of the linear correlations of ΔS^f against ΔS^m_{ideal}, where P = *acetaminophen*, A = *p-acetoxyacetanilide and* W = *water*

Influence of various stirring speeds during crystallization of P crystals grown from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3}

Stirring speed (rpm)	(a) In the presence of 500 mg·dm^{-3} A							(b) In the absence of A					
	$T_m \pm$ S.D. (K)	$\Delta H^f \pm$ S.D. (kJ·mol^{-1})	$\Delta S^f \pm$ S.D. J·K^{-1}·mol^{-1}	$\bar{S}_A$	$\bar{S}_W$	$\bar{S}_P$	ΔS^m_{ideal} (J·K^{-1}·mol^{-1})	$T_m \pm$ S.D. (K)	$\Delta H^f \pm$ S.D. (kJ·mol^{-1})	$\Delta S^f \pm$ S.D. (J·K^{-1}·mol^{-1})	$\bar{S}_W$	$\bar{S}_P$	ΔS^m_{ideal} (J·K^{-1}·mol^{-1})
200	442.1 ± 0.1	27.86 ± 0.36	63.0 ± 0.8	0.090	0.301	0.075	0.466	441.4 ± 0.2	28.14 ± 0.41	63.8 ± 0.9	0.256	0.050	0.306
240	442.1 ± 0.1	27.66 ± 0.21	62.6 ± 0.5	0.085	0.358	0.089	0.532	438.7 ± 0.4	25.90 ± 0.28	59.0 ± 0.6	0.697	0.181	0.878
280	442.1 ± 0.1	27.46 ± 0.20	62.1 ± 0.8	0.084	0.378	0.094	0.556	437.7 ± 0.4	25.26 ± 0.33	57.7 ± 0.8	0.954	0.277	1.231
320	441.9 ± 0.1	27.40 ± 0.06	62.0 ± 0.8	0.081	0.395	0.099	0.575	435.4 ± 0.7	24.39 ± 0.64	56.0 ± 1.4	1.096	0.337	1.433
360	442.0 ± 0.2	27.04 ± 0.21	61.2 ± 0.5	0.080	0.445	0.113	0.638	434.3 ± 0.8	23.76 ± 0.18	54.7 ± 0.4	1.352	0.458	1.810
400	442.0 ± 0.1	27.18 ± 0.15	61.5 ± 0.4	0.079	0.422	0.105	0.606	434.1 ± 0.7	23.13 ± 0.19	53.3 ± 0.4	1.428	0.497	1.925

Correlation coefficient, *r*	[−0.987]	−0.822	[−0.990]	0.972
Standard error of estimate, s_{yx}	[0.122]	0.463	[0.586]	0.862
Slope (− d.i.)	[−11.11]	−11.13	[−6.09]	−6.08
Standard error of slope	[0.91]	1.73	[0.43]	0.32
95% confidence interval of slope	[−13.64 to −8.58]	−14.74 to −7.52	[−7.28 to −4.90]	−6.75 to −5.41
Intercept (ΔS^f_0)	[68.3]	68.3	[65.1]	65.1
Standard error of intercept	[0.5]	1.0	[0.6]	0.4
95% confidence interval of intercept	[66.9 to 69.7]	66.2 to 70.4	[63.4 to 66.8]	64.3 to 65.9
Total number of data points, *n*	[6]	22	[6]	23

Regression parameters and statistics in square brackets are based on the mean values of replicates.

where R is the universal gas constant (8.3143 $J \cdot K^{-1} \cdot mol^{-1}$) and x_P, x_A, and x_W are the mole fractions of the components of the crystals, acetaminophen (P), *p*-acetoxyacetanilide (A) and water (W), respectively.

The "disruption index" (*d.i.*) is defined by the slope, $(b - c)$, of the following derived equation:

$$\Delta S^f = \Delta S_0^f - (b - c) \cdot \Delta S_{ideal}^m \qquad (2)$$

where the intercept, ΔS_0^f, represents the hypothetical entropy of fusion of pure, perfect crystalline sample of P, for which $\Delta S^f = \Delta S_0^f$, if impurity defects are the only, or at least the predominant, defects present.

The assumption of linearity for the relationship between ΔS^f and ΔS_{ideal}^m was checked by examination of (the raw and standardized) residual plots and by replicate measurements (Draper and Smith, 1981). The latter procedure involves: (1) partitioning the residual sum of squares (RSS) into the sum of squares for lack-of-fit and the sum of squares for pure error (calculated from replicate observations); (2) dividing each of these sum-of-squares terms by their respective degrees of freedom to obtain their corresponding mean square values; and (3) testing for significance at the 5% level the ratio of the mean square value for the lack-of-fit to that for the pure error (i.e. *F*-value).

The residual plots for both crystallization cases defined above are generally satisfactory (Figs. 7a and b). Although an unusually high standardized residual is detected in the presence of A, the residuals are more or less randomly distributed about the horizontal line, $\epsilon = 0$, and exhibit no discernable systematic pattern, suggesting that they are not serially correlated and that no additional regressors, e.g. quadratic terms, need be included in the equation. The lack of divergent/convergent trend among the residuals indicates that the assumption of constant error variances is not violated. The *F*-tests for the lack-of-fit yield insig-

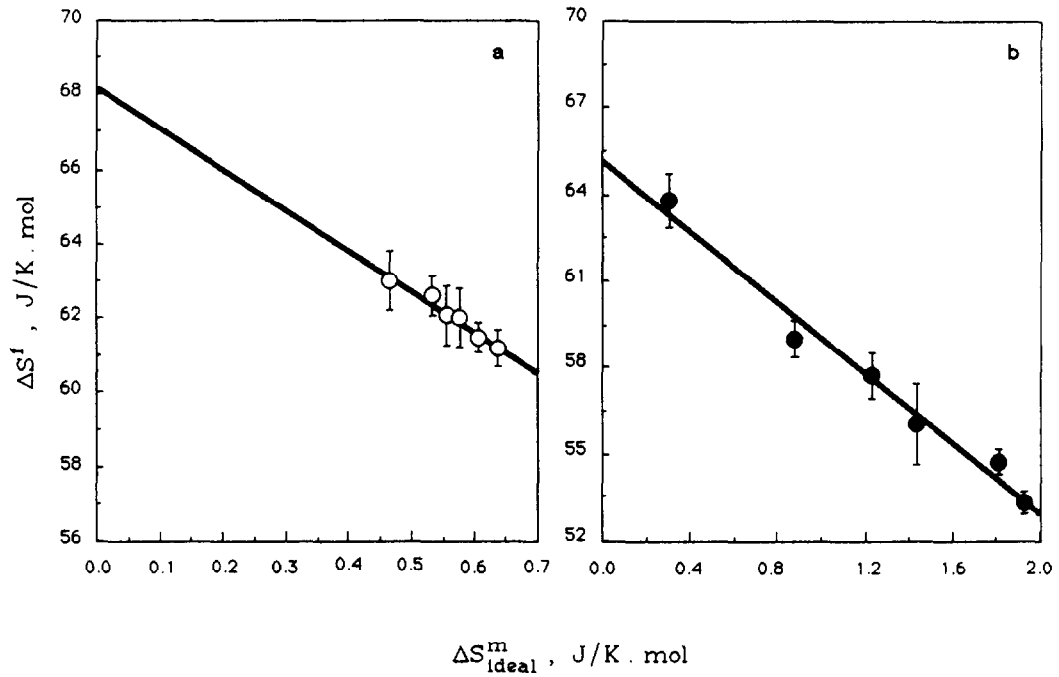

Fig. 6. Linear regression plot of the entropy of fusion, ΔS^f, against the ideal molar entropy of mixing, ΔS_{ideal}^m, for acetaminophen crystals grown in the presence (Fig. 6a, ○, left) and absence (Fig. 6b, ●, right) of 500 $mg \cdot dm^{-3}$ *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 $g \cdot dm^{-3}$ and at various stirring speeds. The vertical bars represent the standard deviations of quadruplicate determinations.

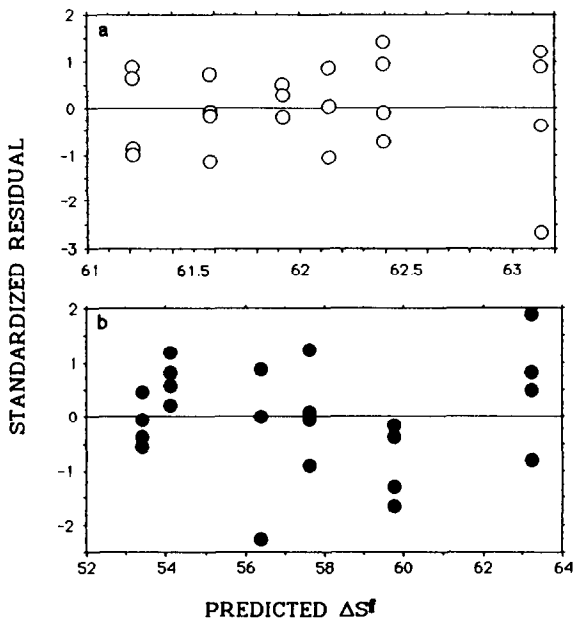

Fig. 7. Standardized residual plots (with respect to the standard deviation of each residual) for the linear regression of the molar entropy of fusion, ΔS^f, on the ideal molar entropy of mixing, ΔS^m_{ideal}, for acetaminophen crystals grown in the presence (○, Fig. 7a) and absence (●, Fig. 7b) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds.

nificant results, suggesting that there is no significant departure from linearity. Further, the slopes and intercepts are statistically significant ($p < 0.05$) and their standard errors are acceptably low, revealing a strong association of ΔS^f with ΔS^m_{ideal}. Thus, the equations expressing ΔS^f as a linear function of ΔS^m_{ideal} adequately describe the data in both cases.

Having been examined for linearity, the equations were compared statistically for significant differences in both the slopes (i.e. the negative values of the disruption index) and intercepts (i.e. ΔS^f_0). For this purpose, the 2-tailed Student *t*-tests as they apply to both regression coefficients were used (Kleinbaum and Kupper, 1978). The negative slopes or *d.i.* based on such analysis were significantly higher for crystals grown in the presence of 500 mg·dm^{-3} A ($d.i = 11.11$) than for those grown from pure aqueous solutions ($d.i = 6.09$), suggesting that the lattice disruption caused by A and/or water is more intense under the former crystallization conditions. It has been demonstrated previously that incorporation of 0.01–0.45 mol% of A and 1.3–4.1 mol% of water into P crystals by varying the concentration of A in solutions led to a *d.i.* of 6.53 (Chow et al., 1985), which is statistically comparable to that obtained in the present work for growth in the absence of A under the influence of varying stirring speeds. This would imply that the incorporated A and water disrupt the crystal lattices of P to the same extent in both cases. (Whilst not explicitly stated in the previous paper, the ΔS^f and ΔS^m_{ideal} data reported therein can also be sufficiently defined by a simple linear relationship, as verified by the approaches outlined above.) That A and water exert greater lattice disruption of the crystals under the mixed influence of 500 mg·dm^{-3} A and of varying stirrer speeds during growth is capable of two interpretations: (1) that the disruptive power of A and water depends not only on their presence and/or concentrations within the crystal lattice, but also on their modes of incorporation; and (2) that the mediating influence of the crystallization variables, the concentration of A and the stirring speed, on the degree of lattice disruption in the P crystals may be additive.

The intercepts (i.e. ΔS^f_0) derived from the above regression analysis might also shed some light on the nature and concentration of lattice imperfections. The intercepts, corresponding to changes in the concentration of A or in the stirring rate along with the addition of 500 mg·dm^{-3} A, are statistically equivalent, being 67.9 and 68.3 J·K^{-1}·mol^{-1}, respectively. However, crystallization involving alteration of the stirring rate alone affords a significantly lower intercept or ΔS^f_0 value. This lower entropy of fusion (i.e. high entropy of the solid state) suggests the coexistence of growth defects of an influentially large but a relatively constant magnitude with the impurity defects in the crystals.

Although substantial variations in the thermodynamic properties of the crystals have been demonstrated, X-ray diffraction failed to show any significant changes in the interplanar spacings (< 0.5%), suggesting that gross crystalline changes (e.g. polymorphs and stoichiometric hydrates) of the crystals have not occurred.

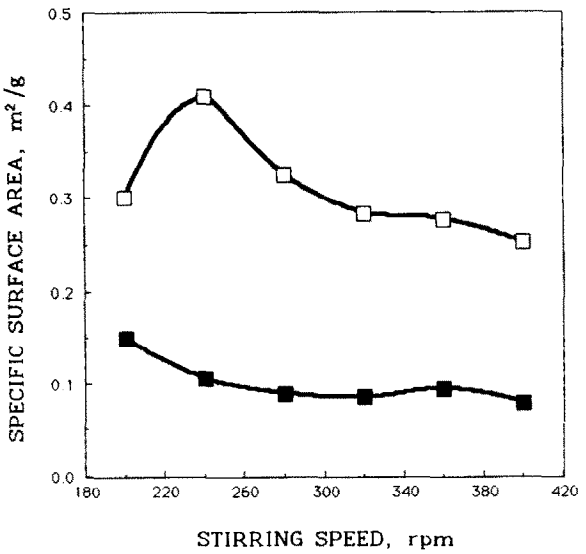

Fig. 8. Specific surface areas of acetaminophen crystals grown in the presence (□) and absence (■) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. Each data point is the mean of duplicate determinations. The variation between measurements is within 7%.

Specific surface area

An increase in the stirring rate of the solutions containing 500 mg · dm^{-3} A augments the SSA of the crystals to a maximum at 240 rpm and then reduces it (Fig. 8). The changes can be seen to be largely related to the tendency of the crystals to form "multiple twins" at low stirring rates. On the other hand, the crystals grown in the absence of A exhibit moderate decreases in SSA with increasing agitation of the solutions (Fig. 8). In addition, these crystals consistently display a much lower SSA than those crystallized with 500 mg · dm^{-3} A at the corresponding stirring rates, consistent with their external morphologies, polygonal prisms and needles, respectively.

Dissolution rate

Increasing the stirring rate during crystallization in the presence of 500 mg · dm^{-3} A increases and then decreases (maxima at 240 rpm) the dissolution rate (*DR*) and the dissolution–time profile of the resulting acicular crystals (Figs. 9a

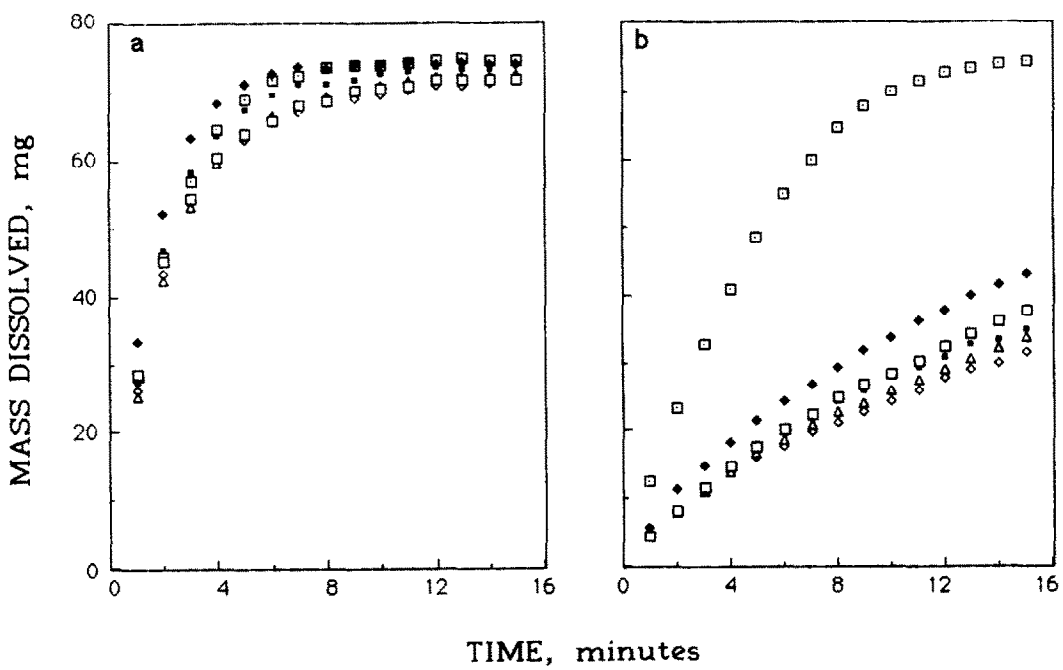

Fig. 9. Dissolution–time profiles of acetaminophen crystals grown in the presence (Fig. 9a) and absence (Fig. 9b) of 500 mg · dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g · dm^{-3} and at the following stirring speeds; (□) 200, (◆) 240, (■) 280, (◇) 320 (△) 360 and (■) 400 rpm. Each data point is the mean of triplicate determinations.

and 10). The change in *DR* appears to mimic that in SSA (Fig. 8), but the change in intrinsic dissolution rate (*IDR*) exhibits an opposite trend (Fig. 11). For the polygonal prismatic crystals prepared in the absence of A, the *DR* and the dissolution-time profile decrease to constant values above 280 rpm with increasing agitation rate during growth (Figs. 9b and 10), in parallel with decreases in SSA (Fig. 8). On the other hand, the *IDR* drops to a minimum at 360 rpm and slightly rises thereafter (Fig. 11). The acicular crystals consistently demonstrate much higher *IDR*s than those of the polygonal prisms, independent of the stirring rate applied during crystallization.

As discussed in our previous paper (Chow et al., 1985), the changes in *IDR* of the P crystals could be linked to a number of well documented key factors including: (1) crystal anisotropy (Burt and Mitchell, 1979; Watanabe et al., 1982); (2) crystal defects induced by A, water and/or crystallization conditions (Burt and Mitchell, 1981); and (3) hydrates (Shefter and Higuchi, 1963). Also of potential importance in this regard are the hydrodynamic conditions during dissolution,

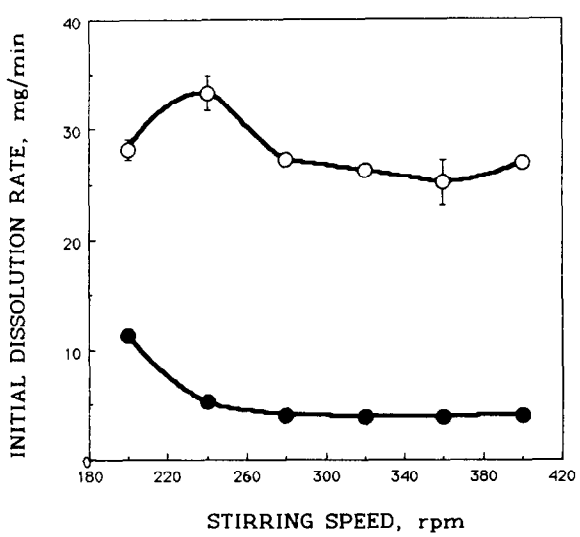

Fig. 10. Initial dissolution rates of acetaminophen crystals grown in the presence (○) and absence (●) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. The vertical bars represent the standard deviations of triplicate determinations.

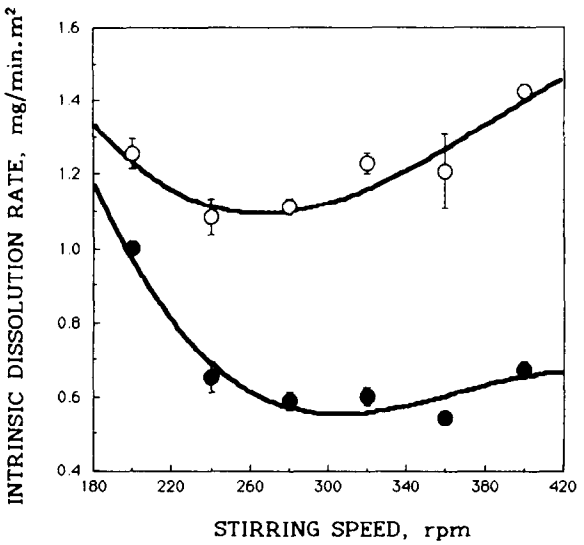

Fig. 11. Intrinsic dissolution rates of acetaminophen crystals grown in the presence (○) and absence (●) of 500 mg·dm^{-3} *p*-acetoxyacetanilide, A, from aqueous solutions at an initial supersaturation of 6.63 g·dm^{-3} and at various stirring speeds. The vertical bars represent the standard deviations of triplicate determinations.

which are closely related to crystal habit. It has been frequently demonstrated that needle-like particles tend to dissolve faster than their non-acicular counterparts (e.g. Burt and Mitchell, 1980; Chow et al., 1985). Although this may be intuitively imputed to a higher geometrical area for the former, it is perhaps not unreasonable to speculate that the hydrodynamic conditions in the vicinity of the particles may vary with the shape of the particles and, thus, may be important in determining the dissolution rate of the particles. However, the relative contribution of this factor to the overall dissolution rate may not be determinable, since it probably overlaps with that from crystal anisotropy and/or crystal imperfections. In the present study, the relatively faster dissolution for the acicular crystals grown in the presence of A may be ascribed to a relative dominance of the high energy faces, more favourable hydrodynamic conditions for dissolution and/or their lower water contents. On the other hand, the decreases in *IDR* for the crystals grown from pure aqueous solutions at 200–360 rpm are consistent with their increases in water content while the increase in

IDR at 400 rpm could result from the greater disruption of the crystal lattice by incorporation of water.

Conclusions

The results of the present study may be summarized as follows.

Higher agitation rates favour the uptake of water but discourage the uptake of A by the crystals, indicating that the former process is essentially transport-controlled while the latter process is predominantly surface-determined.

The changes in the ΔH^f, T_m and ΔS^f are inversely related to the changes in the water content of the crystals, suggesting that water is the major disrupter of the crystal lattice. Although A exerts very little effect on the various thermodynamic properties by itself, it appears to be capable of modulating much larger quantities of water in the crystals and thereby controls their energy and entropy. This is particularly evidenced by the fact that, in the absence of A, the water content of the crystals drastically rises while their ΔH^f, T_m and ΔS^f sharply fall when the solutions are subjected to more intense stirring.

The disruptive influence of A and/or water on the crystal lattice of P, as determined by the "lattice disruption index" (i.e. negative slope derived from the linear regression of ΔS^f against ΔS^m_{ideal}) is quantitatively identical for the crystallization variables, concentration of A and stirring speed. However, in the presence of A (500 mg · dm^{-3}), a change of the stirring speed generates a significantly greater lattice disruption of the crystals, suggesting the presence of defects additional to those induced by A and water in the crystals. These defects may arise mostly from growth, i.e. growth defects, which are expected to be related to the conditions of crystallization.

The morphology of P crystals depends on the stirring rate during growth in the presence of A, but not on the stirring rate during growth in the absence of A.

Considerable differences in dissolution rate of the crystals can still be observed after correcting for the contribution due to surface area, suggesting that factors other than surface area may be involved. Such factors possibly encompass: (a) crystal anisotropy; (b) shape-related hydrodynamic conditions during dissolution; (c) crystal imperfections; and (d) non-stoichiometric hydrates.

The present findings demonstrate the important role played by the agitation rate during crystallization on the physical properties of pharmaceutical crystals, especially when grown in the presence of an additive or impurity. The findings also complement and are consistent with those reported previously (Chow et al., 1985) and further highlight the great influence of A in regulating the habit, water content, lattice energy, lattice disorder and dissolution rate of the P crystals.

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